REMARKS

Claims 2-4 and 17 are pending in the instant application. Claims 1, 5, 8, 11, 12, and 15-16 are cancelled without prejudice or disclaimer. As no amendments are being made to the claims, claims 2-4 and 17 remain pending in the application.

Claim Rejections – 35 U.S.C. § 103

Claims 2-4, 6-10, 13, 14, and 17, which are directed to methods of treating psoriasis featuring a compound of formula (I), are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Johansen et al., *Prog Surg*. 1997 24: 225-231 ("Johansen") in view of Holmeide et al., *J. Chem. Soc., Perkin Trans*. 2000 1: 2271-2276 ("Holmeide"). Claim 8 is cancelled without prejudice or disclaimer, and therefore any rejection against claim 8 is moot. Regarding claims 2-4, 6, 7, 9, 10, 13, 14, and 17, Applicants respectfully disagree with the rejection and request that it be withdrawn.

To establish a *prima facie* case of obviousness, the Examiner must establish that the prior art included each element claimed (M.P.E.P. 2143). In addition, "[a] patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art." *KSR International Co. v. Teleflex Inc*. 167 L. Ed. 2d 705, 712. The Supreme Court in *KSR* reaffirmed the framework for determining obviousness as set forth in *Graham v. John Deere Co*. (383 U.S. 1, 148 USPQ 459 (1966)), but stated that the Federal Circuit had erred by applying the teaching-suggestion-motivation (TSM) test in an overly rigid and formalistic way. However, although a rejection need not be based on a teaching or suggestion to combine, a preferred search will be directed to finding references that provide such a teaching or suggestion if they exist, especially where it is clear that the claimed invention is not a simple substitution, predictable extension or anticipated result of the prior art at the time of filing. M.P.E.P. 2141. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the

Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g., Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

Applicants' invention is based on the observation that enzyme IVa PLA_2 is linked to psoriasis and that specific inhibitors of IVa PLA_2 are useful for treating psoriasis (the specification spanning page 11, line 35 – page 14, line 15; Figures 1-5). The claims, as currently amended, are directed to methods of treating psoriasis by administering to a mammal an effective amount of the compounds of the invention that selectively inhibit enzyme IVa PLA_2, or such methods of treating psoriasis with the result of selectively inhibiting the enzyme IVa PLA_2. Johansen and Holmeide do not teach all the elements of a method of treating psoriasis as claimed, nor do they provide the requisiste motivation or guidance to combine the two references in the manner suggested by the Office Action, and thus do not provide an expectation of success in making and using the invention.

The Office has cited Johansen, stating that: "Johansen et al suggest it would be reasonable to attempt treatment of psoriasis by administering PLA_2 inhibitors." However, nowhere in the cited reference does Johansen specifically link psoriasis to IVa PLA_2. In the absence of any teaching that psoriasis is associated with IVa PLA_2, one of skill in the art would lack the requisite motivation or expectation of success to use IVa PLA_2 for that purpose. Johansen studied just two PLA_2 enzymes (i.e., $npPLA_2$ and $cPLA_2$). Importantly, Johansen did not detect any correlation between levels of $cPLA_2$ and psoriasis (page 227, 3rd full paragraph), let alone any correlation between levels of IVa PLA_2 (a $cPLA_2$ subtype) and psoriasis. It is stated on numerous occasions in Johansen that the expression level of the cytosolic enzyme does not change significantly in psoriatic skin compared to normal skin.

In contrast, the expression level of the $npPLA_2$ enzyme is increased in psoriatic skin compared to normal skin. In previous studies cited by Johansen (page 230, 1st full paragraph), $npPLA_2$ is implicated in psoriasis:

> There is growing evidence that eicosanoids and raised PLA_2 activity are implicated in the pathogenesis of psoriatic lesions [8-10]. ***In a study that supports a central role for nonpancreatic PLA_2 in skin inflammation***, it was shown that intradermal injection of purified $npPLA_2$ induced cellular infiltration, interstitial edema, vascular permeability, and hyperemia [11]. [emphasis added]

Johansen describes a correlation between levels of type II PLA_2, termed $npPLA_2$ (page 226, 4th and 5th paragraph), and psoriasis. Johansen provides the observation that in pustular psoriasis, the $npPLA_2$ levels are consistent with the severity of the disease (page 230, 1st full paragraph). Based on the correlation of the increased levels $npPLA_2$ and the severity of the disease, the disclosures of Johansen would lead one skilled in the art to conclude that $npPLA_2$ is critical in psoriasis. In view of the previous studies cited by Johansen and the disclosures of Johansen that suggests a role for $npPLA_2$ in eiconsanoid production due to over expression, it follows that the logical starting point for the treatment of psoriasis is an $npPLA_2$ inhibitor.

Assuming *arguendo* one were to rely on the disclosure of Johansen, it is worth noting that the compounds of the present invention do not inhibit $npPLA_2$, and they would not be expected to be effective at treating psoriasis (e.g., see Bartoli et al., "Tight Binding Inhibitors of 85-kDa Phospholipase A_2 but Not 14-kDa Phospholipase A_2 Inhibit Release of Free Arachidonate in Thrombin-stimulated Human Platelets." Journal of Biological Chemistry, 269:15625-15630, 1994; "Bartoli"). In Bartoli, the $cPLA_2$ inhibitor $AACOCF_3$ was screened against $cPLA_2$ and $sPLA_2$. Based on the results in Table 1 at page 15626, Bartoli concludes that the *in vitro* inhibition data shows that $AACOCF_3$ is more than 1000 times less potent and inhibitory of $sPLA_2$ than $cPLA_2$.

Regarding the Office's position that any $npPLA_2$ inhibitor could treat psoriasis, Applicants respectfully disagree. In data submitted herewith in Exhibit A, it is shown that the $npPLA_2$ inhibitor BM1 6.2269 does not treat psoriasis. The data in Exhibit A confirms the results presented in Figure 5 of the instant application where it is demonstrated that AKH-217 inhibits luciferase activity in a NF-kB reporter assay with TNFα stimulation. As shown in Exhibit A, HaCaT cells were stimulated with proinflammatory cytokines IL-13 or TNFα. Activation of the transcription factor NF-kB analyzed via luciferase expression is a measure of

inflammation. The data in Exhibit A incorporates the BM16.2269 data for the same test alongside the data presented in Figure 5.

While AKH-217 dose-dependently inhibited luciferase activity, BM16.2269 was ineffective. It is clear then that AKH-217 inhibits luciferase activity to a much greater degree than BM16.2269. This result is important as treatment of psoriasis can be linked to the prevention of activation of NFkB. Thus, BM16.2269 does not reduce inflammation or prevent NF-kB expression. Without wishing to be limited by theory, it is believed that even when the npPLA$_2$ enzyme is inhibited, NF-kB activation still occurs via other similar enzymatic pathways. Due to the high diversity of secretory enzymes, other enzymes may substitute for the activity of any inhibited enzyme. Thus, this result shows that the known npPLA$_2$ inhibitor does not decrease luciferase activity, and inhibition of npPLA2 is not useful for treating psoriasis. Assuming *arguendo* it were reasonable based on Johansen prior to attempt to treat psoriasis using PLA$_2$ inhibitors, it is shown that even by using Johansen's most preferred inhibitor (i.e., BM16.2269) one would not succeed in such treatment.

In fact, Johansen provides no guidance as to which PLA$_2$ enzyme among the numerous PLA$_2$ enzymes should be inhibited. Nor would it be obvious that IVa PLA$_2$ should be selected given that PLA$_2$ enzymes span three protein families and 15 groups (see, e.g., The Rule 132 Declaration by George Kokotos, Ph.D. filed November 17, 2008). In sum, there is no express teaching or even motivation within Johansen for treating psoriasis by inhibiting the enzyme IVa PLA$_2$ or by administering an inhibitor of IVa PLA$_2$

The Office has also cited Holmeide as an alleged remedy for this deficiency of Johansen. But this reliance is misplaced. Holmeide cannot cure the deficiencies of Johansen because, like Johansen, Holmeide failed to recognize that psoriasis is associated with IVa PLA$_2$. The Office Action at page 4 states "...Holmeide et al suggests that Compound 18 would inhibit cPLA$_2$ with a reasonable expectation of success." However, Holmeide also does not recognize that the polyunsaturated trifluoromethyl ketone Compound 18 would selectively inhibit IVa PLA$_2$. Holmeide fails to teach or suggest that Compound 18 or any other compound synthesized therein selectively inhibits IVa PLA$_2$. Holmeide provides no guidance that any individual cPLA$_2$ enzyme among the known groups/subgroups of cPLA$_2$ enzymes (e.g., IVa) is selectively

inhibited by Compound 18. Thus, Holmeide provides no express teaching or even motivation for selectively inhibiting the enzyme IVa PLA_2 using Compound 18.

In further support of the obviousness of the rejection, the Office Action states:

> That Holmeide et al does not appreciate the utility of the compound to selectively inhibit IVa PLA_2 is immaterial to the basis of the rejection. Johansen et al teaches that selective inhibitors for PLA2 enzymes have potential in treating psoriasis, and it would be obvious to try selective PLA_2 enzymes inhibitors, such as those disclosed by Holmeide et al, to treat psoriasis.

Applicants respectfully disagree. In the absence of any mention of enzyme IVa PLA_2 in either of the cited references there is no motivation to combine the cited references in the manner suggested in the Office Action to arrive at Applicants' invention. Holmeide fails to describe selectively inhibiting the enzyme IVa PLA_2, and Johansen fails to provide the crucial link between IVa PLA_2 and psoriasis that would motivate one to look to a selective inhibitor of the enzyme IVa PLA_2 for treating psoriasis in the first place. This link is not found in either of the cited references, but is instead found in Applicants' disclosure.

Regarding the allegation that "it would be ***obvious to try*** selective PLA_2 enzymes inhibitors, such as those disclosed by Holmeide et al, to treat psoriasis" [emphasis added], Applicants respectfully disagree that "obvious to try" is an appropriate standard for determinining obviousness in the present case. In *In re Kubin* (Fed. Cir. 2009), citing *In re O'Farrell* (Fed. Cir. 1988), the court described two classes of situations where "obvious to try" is erroneously equated with obviousness under 35 U.S.C. §103:

> 1) what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful;
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> 2) what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. (citations omitted).

Regarding the first "obvious to try" situation, at the time the application was filed, neither Johansen nor Holmeide gave any indication as to which parameters were critical or any direction as to which of the many possible PLA_2 enzymes was likely to be successful. It would not have been obvious that any of the compounds synthesized by Holmeide would ***selectively*** inhibit IVa PLA_2 based solely on a preliminary ability to inhibit $cPLA_2$. Even among the Group IV PLA_2 family, the biochemical properties and tissue distribution of Group IV PLA_2 enzymes suggests distinct mechanisms of regulation and distinct functional roles (e.g., as reviewed in the post-filing date reference Ghosh et al., "Properties of the Group IV phospholipase A_2 family." Progress in Lipid Research, 45:487-510, 2006). Inhibiting all $cPLA_2$ enzymes would lead to unacceptable side effects.

The compounds of the invention are specific for a particular $cPLA_2$ enzyme, i.e., IVa PLA_2. The compounds of the invention are specific for IVa PLA_2, which is not taught in Holmeide or Johansen. Not only is it surprising that the compounds treat psoriasis but it is also surprising that they do so without causing side effects. Furthermore, the compounds of the invention are directed to specific inhibitors (e.g., X must be CF3; there must be one of 5 heteroatoms beta to the carbonyl group, etc.) and are specific to IVa PLA_2.

In contrast, Holmeide provides no guidance as to which $cPLA_2$ enzyme or subgroup any of the compounds would successfully inhibit. Instead, one would have to test each compound individually against each $cPLA_2$ enzyme individually to determine which $cPLA_2$ enzyme or subgroup could be selectively inhibited. Then one would have to determine which of these enzymes was associated with psoriasis.

The task of identifying a selective PLA_2 inhibitor for the treatment of psoriasis is further compounded without knowledge of which specific PLA_2 enzyme is linked to psoriasis. Johansen provides no guidance as to which PLA_2 enzyme could be selectively inhibited to treat psoriasis. Accordingly, the only possible way one would have been able to arrive at the invention would have been to vary all the parameters or try each of the numerous possible choices until one arrived at a successful result, which is not the legal standard for obviousness under 35 U.S.C. §103. The set of possibilities to try is the product of the combination of

compounds and individual PLA_2 enzymes (to identify a selective PLA_2 inhibitor) multiplied by the combination of individual PLA_2 enzymes with increased levels in psoriatic vs. normal tissue (to identify a specific PLA_2 enzyme to be inhibited in psoriasis treatment). Given the myriad possible combinations that one would need to try in the manner suggested by the Office, it would not be reasonable under the legal standard set forth by the courts to expect success in arriving at Applicants' invention in such a manner. In fact, it is Applicants' disclosure that the selective inhibition of IV PLA_2 enzyme can be used to treat psoriasis that provides the power to narrow the possibilities down to a finite number of identified, predictable solutions.

Regarding the second "obvious to try" situation, Johansen provides an invitation to explore a new technology or general approach. The Office bases its rejection on a statement of Johansen that

> Altogether, selective inhibitors for PLA_2 enzymes should have a potential in curing some of the inflammatory symptoms, including epidermal hyperproliferation due to increased leukotriene production, related to eicosanoid production and cell activation in both epidermis and dermis in psoriasis. [page 230, last paragraph]

The Office Action at page 4 further states: "the teaching quoted above [i.e., page 230, last paragraph of Johansen] suggests that it would have been reasonable to at least ***try*** selective inhibitors for PLA_2 enzymes to treat psoriasis with an expectation of success" [emphasis added]. Applicants respectfully submit that, when read in context, the teaching merely invites experimentation of selective inhibitors for PLA_2 enzymes, which seems to be a promising field for psoriasis treatment according to Johansen. There are numerous PLA_2 enzymes that are encompassed by three protein families, and each individual PLA_2 enzyme is classified according to one of 15 groups and a subgroup. Johansen provides no teaching whatsoever regarding the specific PLA_2 enzyme(s), including $npPLA_2$ or $cPLA_2$, that should be selectively inhibited to treat psoriasis. At best, of the two PLA_2 enzymes characterized, the results described in Johansen might suggest treating psoriasis by inhibiting $npPLA_2$, which displayed increased levels in psoriatic tissue. One of skill in the art, facing the problem of providing a treatment for psoriasis, would not look to $cPLA_2$, or even IVa PLA_2, based on Johansen at the time the

application was filed. Thus, Applicants respectfully submit it would not have been reasonable to assume that administering PLA_2 inhibitors would treat psoriasis based on Johansen. The statement of Johansen provides only general guidance as to the particular form of the claimed invention or how to achieve it, which is not the appropriate standard of obviousness under 35 U.S.C. §103, as consistently upheld by the court.

In sum, neither of the references links IVa PLA_2 to psoriasis and none provides the requisite motivation to use a selective inhibitor of IVa PLA_2 to treat psoriasis. Importantly, none of the cited references provides insight into the surprising and unexpected *in vivo* results observed by Applicants, which showed that inhibitors of IVa PLA_2 inhibit inflammation and are therefore effective for the treatment of psoriasis. This result was unexpected because neither of the references present any *in vitro* or *in vivo* data indicating that any PLA_2 inhibitor would be effective for the treatment of psoriasis, much less that selective inhibitors of IV PLA_2 treat psoriasis without side effects.

In vivo tests have been performed to demonstrate the utility of the claimed compounds in animal models, the results of which Applicants submit herewith in Exhibit B. The data presented in Exhibit B depict the results of AVX001 (i.e., AKH217 as described in the specification) in treating inflammation in the Carrageenan Edema Test (Winter et al., "Carrageenin-induced edema in hind paw of the rat as an assay for anti inflammatory drugs." Proc. Soc. Exp. Biol. Med., 111:544-547, 1962), a model of psoriatic inflammation. This method is used to detect compounds with anti-inflammatory activity. AVX001/AKH217, which was evaluated in the Carrageenan Edema Test, is described in Applicants' specification as a selective inhibitor of IVa PLA_2.

As demonstrated in Exhibit B, the compound AVX001 was effective at reducing inflammation in rats when administered at low doses (~30 mg/kg), especially compared to aspirin (~300 mg/kg). In the control groups administered either vehicle 1 or vehicle 2, the volume of the inflamed paw was increased as compared with that of the non-inflamed paw (vehicle 1: +52%, $p < 0.001$; vehicle 2: +45%, $p < 0.001$), indicating development of edema. No significant difference was observed between the vehicle 1 and vehicle 2 control groups. In contrast, the group of rats administered AVX001 (30 mg/kg), clearly showed a decrease in the

volume of the inflamed paw, as compared with the vehicle 2 control group (-20%, $p < 0.01$). The effect of AVX001 in reducing the volume of the inflamed paw were also observed when AVX001 was administered at 10 or 20 mg/kg. Administration of aspirin (256 mg/kg) clearly decreased the volume of the inflamed paw, as compared with vehicle 1 controls (-32%, $p < 0.001$), although at nearly 10-fold higher dose (AVX001 at 30 mg/kg v. aspirin at 256 mg/kg). Administration of aspirin weakly, but significantly, decreased the volume of the non-inflamed paw (-6%, $p < 0.05$). In contrast to aspirin, AVX001 at any of the doses tested had no effect on the volume of the non-inflamed paw. Altogether, these results show that AVX001/AKH217 has potent and specific anti-inflammatory properties *in vivo*.

Thus, the *in vivo* efficacy of AVX001/AKH217 in treating psoriatic inflammation as shown in Exhibit B were surprising and unexpected and would not have been apparent given the disclosures of Johansen and/or Holmeide.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 2-4, 6, 7, 9, 10, 13, 14, and 17 under 35 U.S.C. §103(a).

CONCLUSION

In view of the foregoing arguments, Applicants respectfully request reconsideration and withdrawal of all pending objections/rejections and allowance of the application with Claims 2-4, 6, 7, 9, 10, 13, 14, and 17 presented herein. If a telephone call with Applicants' representative would be helpful in expediting prosecution of the application, Applicants invite the Examiner to contact the undersigned at the telephone number shown below.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 64490(53385).

Dated: August 18, 2009

Respectfully submitted,

Electronic signature: /Elbert Chiang, Ph.D./
Elbert Chiang, Ph.D.
Registration No.: 60,325
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 517-5502
Attorneys/Agents For Applicant